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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,097	01/28/2004	Francois Lang	BJS-1721-74	9827

23117 7590 03/08/2007

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/765,097	LANG ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/18/06, 1/28/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-16,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/831,019.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 1/28/04 and Applicant's response filed 12/18/06 are acknowledged and have been entered.

2. Applicant's election with traverse of Group I (claims 14-20), and species of MHC class I tetramer wherein at least one amino acid substitution in the α3 domain of the heavy chain in the zone of interaction with CD8 is mutated in Applicant's said response filed 12/18/06.

The basis for Applicant's traversal is of record in the said response on pages 1-3.

Applicant's arguments have been fully considered, but are not persuasive.

It is the Examiner's position that: There are two criteria for a proper requirement for restriction between patentably distinct inventions:

(1) The inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed (see MPEP 806.05 - 806.05(I)); and

(2) There must be a serious burden on the Examiner if restriction is not required (see MPEP 803.02 806.04(a) - (j), 808.01(a) and 808.02).

Regarding undue burden, the M.P.E.P. 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search."

The restriction requirement enunciated in the previous Office Action meets this criterion of serious burden and therefore establishes that serious burden is placed on the Examiner by the examination of added groups. The inventions are distinct for reasons elaborated in paragraphs 2, 4 and 7 of the previous Office Action.

With regard to Applicant's arguments to the species restriction, it is the Examiner's position that each of the species is distinct because they have different structures, and a search of different species would necessitate different searches and be unduly burdensome, *i.e.,* a mutation of an α3 domain amino acid residue is a different field of search from a chemical modification of an α3 domain amino acid residue, and both are different fields of search from a deletion of an α3 domain amino acid residue. Election of species should not be required over species that are considered clearly unpatentable (obvious) over each other. See MPEP 806.04. Applicant is invited to provide a statement on the record if Applicant considers the species obvious over each other.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-16, 19 and 20 read on the elected species.

Accordingly, claims 17, 18 (non-elected species of Group I) and claims 21-26 (non-elected groups II-III) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 14-16, 19 and 20 are presently being examined.

3. The amendment filed 1/28/04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The incorporation by reference of PCT/FR00/02443 because the preliminary amendment was not mentioned in the declaration (filed in the 09/831,019 parent application). Applicant is required to cancel the new matter in the reply to this Office Action.

4. The disclosure is objected to because of the following informalities:

a. The abstract of the disclosure has a spelling error, *i.e.,* "recombinant proteins analogues."

b. The use of the trademark DYNABEADS has been noted in this application on page 15 at line 32. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

c. There is no brief description of the drawings for Figures 1-7.

d. The first line of the specification should be updated to include the status, *i.e.,* abandoned, of parent application serial no. 09/831,019.

Appropriate correction(s) is/are required.

5. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 14-16, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed multimer recited in base claim 14, and including those recited in the dependent claims, built up from recombinant protein analogues of Class I MHC characterized in that the proteins comprise at least one modification in the zone of interaction of a heavy chain with the CD8 co-receptor leading to a reduction, or even suppression, of the affinity of the interaction between the heavy chain and CD8.

The instant claims encompass tetramers of MHC class I wherein a modification, including a mutation, is made in at least one of the α3 domain amino acid residues of the MHC class I heavy chain that interacts with CD8, such that there is a reduction or suppression of the affinity of interaction between the heavy chain and CD8. There is insufficient disclosure in the specification of a method using said exogenous compound.

The specification discloses that an example of a mutation in the α3 domain of the heavy chain is A245V (page 5 at lines 16-18).

The specification does not disclose what the zone of interaction of a heavy chain with the CD8 co-receptor is, nor what mutations or other modifications are sufficient to confer the property of reducing or suppressing the CD8/heavy chain affinity of interaction.

One of skill in the art would not have recognized that Applicant was in possession of the necessary common attributes or features possessed by the members of the genus.

9. Claims 14-16, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed multimer built up from recombinant protein analogues of Class I MHC characterized in that the proteins comprise at least one modification in the zone of interaction of a heavy chain with the CD8 co-receptor leading to a reduction of the affinity of the interaction between the heavy chain and CD8, does not reasonably provide enablement for the said multimer wherein the modification leads to suppression of the affinity of interaction between the heavy chain and CD8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass making and/or using the multimer with the said modification that leads to suppression of the affinity of interaction between the heavy chain and CD8. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed multimers can be made and/or used.

The specification discloses that an example of a mutation in the α3 domain of the heavy chain is A245V (page 5 at lines 16-18). The specification discloses that the multimers may be used for detection and/or isolation of peptide-specific CD8+ T cells or in diagnosis and therapy (page 4 at lines 29-32). The specification discloses that the multimers with reduced binding to CD8 may be used *in vitro* to reduce background noise in immunofluorescence analysis or flow cytometry of T cell binding to class I MHC tetramers (page 2 at lines 9-32, page 3 at lines 1-12).

The specification does not disclose what the zone of interaction of a heavy chain with the CD8 co-receptor is, nor what mutations or other modifications are sufficient to confer the property of reducing or suppressing the CD8/heavy chain affinity of interaction, other than the A245V mutation. The specification does not disclose how a multimer comprising at MHC class I complexes comprising at least one α3 modification or mutation sufficient to suppress affinity of binding between class I MHC heavy chain and CD8 is to be used either *in vitro* or *in vivo*, nor does it provide any working examples of such.

Evidentiary reference Gao *et al* (Nature. 1997, 387(6633): 630-634) teach that CD8αα binds one HLA-A2/peptide molecule, interfacing with the α2 and α3 domains of HLA-A2 and also contacting β2m. A flexible loop of the α3 domain (residues 223-229) is damped between the complementarity determining region-like loops of the two CD8 subunits in the classic manner of an antibody-antigen interaction, precluding the binding of a second MHC molecule. The position of the α3 domain is different from that in uncomplexed HLA-A2, but no conformational change extends to the MHC /peptide surface presented for TCR recognition. Thus, the said reference teaches that other domains of heavy chain as well as β2m light chain interact with CD8. Gao *et al* further teach that one human allele, HLA-Aw68, has been reported to show an aberrantly low

level of CD8 binding, and effect that has been linked to polymorphism at residue 245 (A245V, the same mutation disclosed in the instant specification). Gao *et al* teach that although there is no direct contact between CD8aa and residue 245, mutation of this residue in HLA-A268 leads to significant distortion of the 223-229 loop from the conformation seen in all other structurally characterized alleles and required for binding to CD8 (especially abstract and paragraph spanning columns 1 and 2 on page 632).

Evidentiary reference Schwartz and Kipnis (The Neuroscientist. 2002, 8(5): 405-413) teach that the effect of treatment of autoimmune disorders should be immunomodulatory rather than immunosuppressive (especially abstract).

There is no guidance in the specification as to what alterations in the α3 domain of an MHC class I heavy chain result in a functional mutant that suppresses interaction of MHC class I with CD8. The one disclosed mutant A245V results in reduced binding. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions or other modifications would be acceptable to confer the functional property of suppression, and to determine how a functional mutant would be used, it would require undue experimentation to identify, make and use such a functional mutant. The enablement provided by the specification is not commensurate with the scope of the claims.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 14-16, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 14 is indefinite in the recitation of "Multimers" because a product should be claimed in the singular.

b. Claim 14 is indefinite in the recitation of "proteins analogues" because it is not clear what is meant, *i.e.,* if Applicant means "protein analogues."

c. Claim 14 is indefinite in the recitation of "at least one modification in the zone of interaction of a heavy chain with the CD8 co-receptor of T lymphocytes" because it is not clear what is meant, *i.e.,* what the zone of interaction is.

d. Claim 14 is indefinite in the recitation of "Multimers built up from recombinant proteins analogues" because it is not clear what is meant, *i.e.,* how "built up from" relates the multimers and the recombinant protein analogues, or what built up means.

e. Claims 14 and 15 are indefinite in the recitation of "modification" because it is not clear what is meant, *i.e.,* substitution, truncation, deletion, chemical alteration, mutation, addition.

f. Claim 14 is indefinite in the recitation of "reduction, or even suppression" because the metes and bounds of the said claim are not clear.

g. Claim 15 is indefinite in the recitation of "characterized in that the modification relates to the α3 domain of the heavy chain" because it is not clear what is meant, *i.e.,* what "relates" means.

h. Claim 19 is indefinite in the recitation of "in that they are in the form of complexes with antigenic peptides" because it is not clear what is meant, *i.e.,* if the multimers are in complex with antigenic peptides or the MHC class I/β2m constituents of the multimers are in complex with antigenic peptides.

12. For the purpose of prior art rejections, the filing date of the instant claims 14-16,19 and 20 is deemed to be the filing date of PCT/FR00/02443, *i.e.,* 9/5/00, as an English language translation of the foreign priority document FR 9911133 has not been provided by Applicant.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 14-16, 19 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Bodinier *et al* (Nature Medicine. 6/00, 6(6): 707-710.

Bodinier *et al* teach tetramers comprised of MHC class I with a mutation of alanine residue 245 to valine in the α3 domain of HLA-A*0201, wherein said mutation produces a reduction of the interaction of the MHC class I heavy chain with CD8, *i.e.,* leading to a reduction of the affinity of interaction between the heavy chain of Class I MHC and CD8, and wherein the MHC complexes were loaded with an antigenic peptide (see entire article).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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